

**Remarks**

Claims 1-33 are pending. Claims 14-20 and 29-33 have been withdrawn. Claims 1-13 and 21-28 are under consideration.

**Objections to the Specification**

The Examiner has objected to the Title of the application as not being descriptive. In particular the Examiner indicates that "applicant should restrict the title to the claimed invention." Applicants have amended the Title of the application to more properly reflect the claims under consideration. Applicants respectfully request the objection be withdrawn.

The Examiner has objected to the application under 37 CFR 1.72(b) as not containing an abstract on a separate sheet as required. Applicants respectfully submit that the present application is a national stage application under 35 U.S.C. 371 and the rules regarding abstracts for applications submitted under 35 U.S.C. 371 are further illuminated under MPEP 1893.03(e) with respect to the rules for abstracts under 37 CFR 1.52(b) which refers to 37 CFR 1.72(b).

Applicants note that according to MPEP 1893.03(e):

When the international application is published as the pamphlet, the abstract is reproduced on the cover page of the publication, even though it appears on a separate sheet of the international application in accordance with PCT Rule 11.4(a). Thus the requirement of 37 CFR 1.52(b) that the abstract "commence on a separate >physical< sheet >or electronic page<" does not apply to the copy of the application (pamphlet) communicated to the designated Offices by the International Bureau under PCT Article 20. Accordingly, it is improper for the examiner of the U.S. national stage application to require the applicant to provide an abstract commencing on a separate sheet if the abstract does not appear on a separate sheet in the pamphlet.

Applicants believe this objection to be moot in light of the above citation and respectfully request the objection be withdrawn.

The Examiner has objected to the specification for failing to designate trademarks by capitalization or the presence of a "TM" or "®" symbol. Applicants have amended the specification to note trademarks where necessary. Applicants respectfully request this objection be withdrawn.

**35 U.S.C. 112, first paragraph**

Claim 10 has been rejected under 35 U.S.C. 112, first paragraph, for allegedly lacking enablement. In particular, the Examiner has rejected claim 10 for listing UCHT1-CRM9 immunotoxin which is allegedly not “known and readily available to the public or obtainable by a repeatable method as set forth in the specification.” Applicants respectfully traverse this rejection. Applicants respectfully remind the examiner that applicants are not required to teach what was already known to those of skill in the art. *In re Buchner* 929 F.2d 660, 661 (Fed. Cir. 1991). Applicants note that the UCHT1-CRM9 immunotoxin has been the subject of numerous patents and publications including, for example, U.S. Patent Nos. 5, 167,956 (the ‘956 patent) and 5,725,857 and PCT publications WO 98/39425 and WO/98/39363 which are describe on page 11, lines 9-11 and incorporate by reference for their teachings of the disclosed immunotoxin. Applicants further note that UCHT1-CRM9 was the subject of the ‘956 patent which issued on December 1, 1992. Thus, the element “UCHT1-CRM9” was known in to those of skill in the relevant art at least as of the issue date of the ‘956 patent and more importantly by the time the present application was filed. Moreover, the element “UCHT1-CRM9” was the subject of several publications which describe how this anti-CD3 immunotoxin is made and some of its properties (see Neville et al. (1989) *J. Biol. Chem.* 264:14653-61 and Neville et al. (1992) *PNAS* 89:2585-89 both of which are enclosed herein as Exhibits A and B respectively). Therefore, not only was the anti-CD3 immunotoxin known, but it was readily obtainable by those of skill in the art by a repeatable method. As indicated above, Applicants are not required to teach what was previously known in the art (i.e., how to obtain the claimed immunotoxin). Applicants believe this rejection to be overcome and respectfully request its withdrawal.

**35 U.S.C. 112, second paragraph**

Claim 10 has been rejected under 35 U.S.C. 112, second paragraph, for allegedly being indefinite. In particular, the Examiner has rejected claim 10 because allegedly the “recitation ‘UCHT1-CRM9’ is merely a laboratory designation which does not clearly define the claimed product.” Applicants respectfully traverse the rejection. Applicants specifically describe the UCHT1-CRM9 immunotoxin as a fusion protein comprising a diphtheria toxin moiety and a targeting moiety directed to the T cell CD3e epitope fused by a GlySer linker on page 11, lines 9-23. Applicants further describe the targeting moiety on page 12, line 23 through page 12, line 11.

Applicants describe the immunotoxin CRM9 as a full length diphtheria toxin with two point mutations at least on page 13, lines 22-31. Thus, applicants clearly and precisely describe what is meant by UCHT1-CRM9. Moreover, Applicants respectfully point out that UCHT1-CRM9 is not a laboratory designation as the examiner indicates but an art understood name for a particular anti-CD3 immunotoxin. The designation of the anti-CD3 immunotoxin is a derivation of the particular immunotoxin mutant used, CRM9, and the clone of the anti-CD3 antibody used, UCHT1. The name CRM9 was first used in by Hu and Holmes in 1987 as a designation for a particular diphtheria toxin mutant (Hu, VW and Holmes, RK (1987) *Biochim Biophys Acta* 902(1):24-20 abstract for which is enclosed herein as Exhibit C). The anti-CD3 antibody UCHT1 was commercially available from Oxoid USA at least as early as 1989 and was described by Neville et al. in two publications which use the term UCHT1-CRM9 (or “anti-CD3-CRM9” where the anti-CD3 portion of the immunotoxin is UCHT1) (see Exhibits A and B and Neville et al. (1995) *J. Biol. Chem.* 270:28037-41 (enclosed herein as Exhibit D)). Thus, as evidenced by its use in the relevant art, “UCHT1-CRM9” is a clearly defined product which is easily within the understanding of those of skill in the relevant art. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

**35 U.S.C. 103(a)**

Claims 1-13 and 21-28 are rejected under 35 USC 103(a) as allegedly being obvious over Neville et al. (U.S. Patent No. 6,103,235) in view of Sykes et al. (U.S. Patent No. 6,514,513) and/or Gray et al. (U.S. Patent No. 6,754,334) and in further view of Strom et al. (in Therapeutic Immunology, edited by Austen et al., Blackwell Science, Cambridge MA, 1996 p451-6). Applicants respectfully traverse the rejection. In order to establish a *prima facie* case of obviousness, the Examiner must show that 1) there is some suggestion or motivation in the references themselves or in the general knowledge of the art to combine or modify the references, 2) there must be a reasonable chance of success, and 3) the prior art must teach or suggest all the limitations of the claim. Applicants respectfully assert that the first prong has not been met. With respect to motivation or suggestion to combine the references, the Examiner asserts that Strom et al. provides the motivation for this combination. Specifically, the Examiner states that “Strom notes the known multi-tiered approach to immunosuppressive therapy in that several agents are used simultaneously.” Applicants note that Strom et al. does not suggest or discuss the particular

the particular combination claimed herein. Thus, at best, Strom et al. can be used as evidence that it would be obvious to try various immunosuppressive therapies to find a combination that provides improved results. However, as noted in MPEP 2145, “obvious to try” is an improper standard under 35 USC 103. This situation is analogous to the situation described by the court in *In re O'Farrell* 853 F.2d 894, 903 (Fed. Cir. 1988). Specifically the court stated that:

In some cases, what would have been ‘obvious to try’ would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was ‘obvious to try’ was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Here, Strom et al. discloses that a multi-tiered approach may be successful, but does not provide guidance as to which combination should be tried and, in particular, does not suggest the combination of an anti-CD3 immunotoxin and costimulation blockade. The Examiner also suggests that Neville et al., Sykes et al., and Gray et al., “describe the known use of combination therapy.” However, it should be noted that none of the references describe the particular combination claimed. In fact, Neville et al., describes only the use of the anti-CD3 immunotoxin with general immunosuppressive agents such as cyclosporine. Sykes et al., describes co-stimulation blockade for immunotherapy, but only mentions multi-tiered treatments involving multiple co-stimulatory blockers (column 38, lines 20-44) or “agents which inhibit the production, levels, or activity of antibodies in the recipient” (column 39, lines 35-40). Likewise, Gray et al. only describes a “multi-tiered” approach with respect to multiple co-stimulation blockers (column 22, lines 38-42). Thus, even if the general guidance to try various combinations provided by Strom et al. is deemed not necessary to provide motivation to combine, what little guidance that is provided by Neville et al., Sykes et al., or Gray et al., is not directed to the particular combination claimed. Moreover, the failure of all of Strom et al., Sykes et al., or Gray et al., to suggest a combination or multi-tiered approach that includes immunotoxins indicates that the claimed combination therapy was outside the mainstream of the art and thus not obvious. Furthermore, “the mere fact that references can be combined or modified does not render the resultant combination obvious.” *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990). For at least these reasons, the

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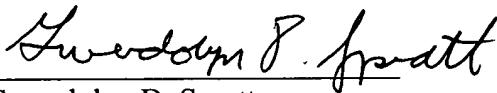
1990). For at least these reasons, the Examiner has failed to establish motivation to combine the references and thus failed to establish a claim of obviousness. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No payment is believed to be do; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

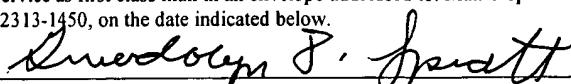
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